## REMARKS/ARGUMENTS

After entry of this amendment claims 42-47, 49, 50, 56-63, 66-76, 83-88 and 90-92 remain pending in this application. Applicants have canceled claims 89 and 93-113 without prejudice. Applicants reserve the right to pursue such claims in a continuation or divisional application.

### Claims 89 and 93-113

Claims 89 and 93-113 were objected to under 37 CFR 1.75 as being a substantial duplicate of claims 42-47, 49, 50, 56-63, 66-68, and 90-92. On the contrary, Applicants can claim their invention with any wording they choose, as it is a matter of opinion whether a claim is a substantial duplicate. Claims 89 and 93-113 were also rejected under 35 USC § 112 for lacking written description for methods to generally make a cell. Applicants note that the specification provides an ample description of methods to make cells, including, embryonic cells, such as stem and germ cells, which can be differentiated into various cell populations, for example, but not limited to, on page 1 (lines 15-20) and page 3 (lines 10-23) of the specification. However, to facilitate prosecution and allowable subject matter, Applicants have canceled claims 89 and 93-113 and intend to file a continuation application to pursue these claims.

### Claims 42-47, 49, 50, 56-63, 66-76, and 83-113:
### Rejection Under 35 U.S.C. § 112, 1st Paragraph

The Examiner has rejected claims 42-47, 49, 50, 56-63, 66-76, 83-113 under 35 U.S.C. § 112, first paragraph as lacking enablement based on the Examiner's assertion that undue experimentation is required to practice the full scope of the claims. Claims 89 and 93-113 were also rejected under 35 USC § 112. These claims have been canceled without prejudice.

The Examiner acknowledges that the specification is enabling for methods of reconstituting an animal embryo by (i) transferring a donor nucleus from a diploid somatic cell into a first recipient oocyte; (ii) removing the nucleus from the first recipient oocyte; (iii) either activating a second recipient oocyte or enucleating a fertilized zygote; and (iv) transferring the nucleus from the first recipient oocyte into the preactivated second recipient oocyte or the enucleated fertilized zygote. However, the Examiner asserts that the specification does not reasonably provide enablement for methods to make any animal embryo or to use the resulting

embryo in methods to make any animal. Applicants note that reconstituted embryos can have other uses besides producing an animal. For example, page 3, lines 10-16; of the specification teach that the reconstituted animal embryos can be used to produce embryonic stem cells, embryonic germ cells, or other desired specialized or unspecialized cell type, e.g., neurons.

To support the lack of enablement rejection to make any animal embryo or to use the resulting embryo in methods to make any animal, the Examiner cites to a research article by Simerly et al. (Science 2003 300:297), as well as a commentary on Simerly's article by Vogel (Science 2003 300:225-227). The Examiner asserts that these articles establish the "art-recognized inability to generate a primate clone through methods of nuclear transfer". The Examiner concludes that since the instant specification fails to provide teachings to show that primate nuclear transfer using the claimed methods would result in pluripotent mammalian cells, it would require undue experimentation. Applicants respectfully disagree. In fact, Hwang et al. (Science. 2004 Mar 12; 303(5664):1669-74. Epub 2004 Feb 12; Attachment A) reported the derivation of a pluripotent embryonic stem (ES) cell line (SCNT-hES-1) from a cloned human blastocyst via somatic cell nuclear transfer. According to Steadman's Medical Dictionary (26$^{th}$ Edition, 1995), a blastocyst refers to the modified blastula stage of mammalian embryos. Thus, primate embryos and primate pluripotent mammalian cells derived therefrom have been produced via nuclear transfer.

In response to the Examiner's rejection that the specification does not reasonably provide enablement for methods to use the resulting embryo in methods to make any animal, Applicants attach hereto another technical comment on Simerly's article by Lanza et al. (Science 2002 301: 1482b; Attachment B). Lanza et al. comment that while Simerly et al. presented new data in their paper, they believe that Simerly et al. overstated their conclusions. In particular, Lanza et al. note that Simerly et al. transferred "only 33 rhesus embryos into 16 surrogates and concluded that reproductive cloning in primates may be unachievable". Lanza et al. further comment that "In our hands, it took dozens of embryos to generate Dolly, more than 150 embryos to generate the first cloned mouse pup and 586 embryos to establish the first two pregnancies in pigs." Lanza et al.'s comments reflect the art recognized fact that it can routinely require hundreds or thousands of embryo transfers to produce a viable cloned animal Also attached hereto is a table developed by Dr. Wilmut (one of the scientists that cloned Dolly) at the Roslin Institute (Somatic Cell Nuclear Transfer Cloning Efficiency" Paterson & Wilmut: www.roslin.ac.uk/public/webtablesGR.pdf; Attachment C). This table provides data on the

cloning efficiency of somatic cell nuclear transfer in seven different animals using multiple cell types and reveals that cloning efficiencies can be as low as 0.1%, which represents 1 live birth per 1000 embryos transferred to surrogate mothers. Interestingly, just last month, on August 3, 2005, the birth of the first cloned dogs was announced. Lee et al. (Nature. 2005 Aug 4; 436(7051):641; Attachment D) reported the cloning of two Afghan hounds by nuclear transfer from adult skin cells. Prior to Lee et al.'s success, failed attempts at cloning dogs were reported (Westhusin et al. 2001 J Reprod Fertil Suppl 57: 287-293; Attachment E) and many in the art doubted whether it could be achieved. However, Lee et al. were successful in producing two cloned dogs by transferring 1095 embryos into surrogate mothers. Furthermore, to date, at least 15 different animals have been cloned via nuclear transfer (see Table 1 below).

**Table 1:**

| **Animal Cloned** | **Reference** |
|---|---|
| Mice | Wakayama et al. (1998). Nature, 394, 369-374; |
| Sheep | Schnieke et al. (1997), Science, 278, 2130-2133. |
| Pig | Polejaeva et al. (2000). Nature, 407, 86-90 |
| Cattle | Kato et al. (1998). Science, 282, 2095- 2098 |
| Goat | Keefer et al. (2000). Biology of Reproduction, 62, 218, Suppl 1. |
| Cat | Shin et al. (2002). Nature 415, 859 |
| Rabbit | Chesné et al.(2002). Nature Biotechnology 20, 366-369. |
| Horse | Galli et al. (2003) Nature 424: 635 |
| Rat | Zhou et al. (2003) Science 302: 1179 |
| Mouflon | Loi et al. (2001)Nat Biotechnol. (10):962-4. |
| Deer | Press release |
| Mule | Woods et al. (2003) Science 301: 1063 |
| Buffalo | Press release |
| Zebrafish | Lee et al. (2003) Nature Biotech 20: 795 |
| Dog | Lee et al. (2005) Nature436(7051):641 |

Thus, Applicants believe that it would not require undue experimentation to practice the claimed invention. One skilled in the art recognizes that the successful cloning of animals is an inefficient process, which is taken into account by establishing an appropriate experimental design. Despite the fact that it could require hundreds or thousands of embryo transfers, this can routinely be accomplished by those skilled in the art in several weeks, and therefore doe not require "undue" experimentation.

It is respectfully believed that this application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is authorized to charge any fees due in connection with this response to Deposit Account No. 11-0980.

Respectfully submitted,
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